A DFT Analysis of the Molecular Structures and Vibrational Spectra of Diphenylsulfone and 4,4′-Sulfonyldianiline (Dapsone)

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We have performed density functional calculations with the B3LYP functional and a 6-311G** basis set to obtain the vibrational spectra in harmonic approximation of the anti-leprosy drug Dapsone and the parent compound diphenylsulfone. Although the chemical difference between the two molecules is not that pronounced (Dapsone has amino groups in the *para* positions in the phenyl rings), Dapsone is an active drug, while to our knowledge diphenylsulfone shows no medical activity. We compared the theoretical results to experimental vibrational spectra found in the literature. With the help of the program GAUSSVIEW we were able to assign the experimentally found spectral lines to specific atomic motions. The remarkable difference between the two molecules, regarding their structural behavior, is that the drug Dapsone has a more flexible structure of the phenyl ring than the parent molecule has. This might contribute to a greater ability of the drug to fit into receptor sites in a cell membrane although one has to be well aware that this plays most propably only a minor role in the drug activity of Dapsone.

Key words: Conformational Behavior, Vibrational Spectra and Assignments, Diphenylsulfone, 4,4′-Sulfonyldianiline, Dapsone

Introduction

The interesting structure of aniline was the subject of many theoretical and experimental studies, and the pyramidal conformation of its nitrogen atom is well established in the literature [1 – 5]. The non-planarity was reported to be a result of a balance between two opposing forces: the *p*-*p* conjugation of the nitrogen lone pair with the aromatic ring and the energy gained from highly directed sp^3 orbitals for the C–N bond formation [1]. A symmetric near-planar structure with C_s molecular symmetry and an HNCC torsional angle (angle between the NH and the CC bonds as viewed along the NC bond) of about 20 degrees was predicted on DFT-B3LYP, MP2, MP4(SDTQ) and CCSD(T) levels of calculations with a 6-311G** basis set to be a real minimum on the potential surface of aniline [5]. At this low-energy form, the two N–H bonds are directed symmetrically towards the same side of the benzene ring. The NH_2 inversion barrier was predicted at the MP2 level of theory to be 2.1 kcal mol^{-1} [5].

On the other side of the N atom the lone pair has the right direction to overlap with the π^* orbitals of the ring. In this way the aromaticity of the phenyl group is not much reduced, and the electrons donated from the -NH_2 group into the antibonding π^* system stabilize the molecule due to this negative hyperconjugation effect. Such a negative hyperconjugation has been described by Wojciechowski *et al.* [1] in their analysis of the natural bond orbital interactions in aniline. Further it is indicated by the slight lowering of the pyramidalization of the -NH_2 group. Note that the above arguments hold also when the benzene ring H atoms next to the -NH_2 group are substituted by Cl atoms [5].

The *planar* structure of aniline was reported to be a clear transition state, since in a *planar* -NH_2 group the lone pair at nitrogen would be of purely $2p_z$ character, and thus it would be involved in conjugation with the phenyl ring. Such a conjugation would certainly stabilize the *planar* -NH_2 group, but would destabilize the molecule as a whole, since conjugation would drastically reduce the aromatic character of the phenyl ring as for example in the aniline radical cation where, due to conjugation, the phenyl ring has an almost quinoidal character [1]. Thus the *planar* form (with a planar NH_2 group) was reported to be a transition state of the -NH_2 inversion [5].

As a continuation of the investigations of the properties of substituted anilines we investigated the conformational stability and analyzed the vibrational spectra of the important sulfa drug Dapsone (4,4′-sulfonyldianiline) in the present study. The work was extended to diphenylsulfone as the main building block of Dapsone for the purpose of comparison. Further we were interested in the question whether or not there are clear differences in the vibrational behavior of the two molecules which might be a minor part of the reason why one of them (Dapsone) is a drug, while the other one (diphenylsulfone) to our knowledge shows no such medical activity. The reason is probably not an electronic one, since as outlined below the structure does not allow a back donation of electron density from the oxygen lone pairs into the antibonding part of the aromatic system. However, as discussed already for aniline, the lone pair on the nitrogen atoms should make the rings more electron rich than those in diphenylsulfone, which might well contribute to the medical activity of Dapsone. Density Functional B3LYP and *ab initio* MP2 calculations were employed in the study. The 6-311G** basis set was utilized in these calculations. The energies of the compounds in their stable conformations and the transition states were optimized at the two levels of calculation. The vibrational frequencies of both molecules in their ground-state structure were calculated at DFT-B3LYP level. The calculated wavenumbers are compared to experimental results. Complete vibrational assignments of the calculated normal modes were made on the basis of the results of GAUSSVIEW visualizations of calculated normal modes and experimental data, since it is of importance to have a clear knowledge, to what motions of atoms an observed vibrational line belongs and what might be the reason if during a modification a line would become diminished or enhanced.

Computational Details and Minimum Structures

The GAUSSIAN 03 program [6], running on a 128 node High-performance e-1350 IBM Cluster, was used to carry out the DFT-B3LYP and the MP2 calculations. The 6-311G** basis set was employed to optimize the structures and predict the energies and the dipole moments of diphenylsulfone and 4,4′-sulfonyldianiline in their possible structures (Fig. 1). The optimized structural parameters (on DFT level only) and energies of the molecules at the DFT-B3LYP and MP2 levels are listed in Tables 1 and 2, while the calculated minimum structure and atom numbering of Dapsone (in diphenylsulfone the $N_{20}H_{26}H_{27}$ group is replaced by H_{20} and the $N_{25}H_{28}H_{29}$ group by H_{25}, while the structures of the diphenylsulfone parts are rather similar in both molecules) is shown in Fig. 1. As is obvious from Table 1, the few comparable X-ray structure data from ref. [7] for diphenylsulfone agree rather well with our calculated ones, given that solid-state effects are absent in our calculations. Further, as is also obvious from Table 1, we conclude that DFT together with our basis set yields a very reliable structure also for Dapsone as compared with the X-ray data [8]. Actually, the most noticeable discrepancies regard the H atom positions which are ill-defined in the experimental structure determination (film data). The poor data set used for the crystal structure determination might also be responsible for differences in bond lengths and angles observed in the phenyl rings [8].

Table 1. Calculated (DFT) and experimental structural parameters for diphenylsulfone (X denotes H) and 4,4′-sulfonyldianiline (X denotes N), rotational constants and dipole moments (see Fig. 1 for atom numbering).

	Diphenylsulfone		4,4′-Sulfonyldianiline	
	calculated	experimental [7]	calculated	experimental [8]
Bond lengths (Å)				
S_1O_4	1.47	1.449	1.47	1.45
S_1C_3	1.81	1.764	1.79	1.76
C_3C_{11}	1.39		1.39	1.37
$C_{11}C_{13}$	1.39		1.39	1.40
$C_{13}C_{15}$	1.39		1.41	1.38
$C_{15}X_{25}$	1.08		1.38	1.39
$N_{25}H_{29}$	–		1.01	1.0
$C_{11}H_{21}$	1.08		1.08	1.1
$C_{13}H_{23}$	1.08		1.09	1.0
Bond angles (deg)				
$O_4S_1C_3$	107.4	108.6	107.2	108.1
$S_1C_3C_{11}$	119.2		119.9	117.8
$C_3C_{11}C_{13}$	118.9		119.9	117.8
$C_{11}C_{13}C_{15}$	120.1		120.7	119.8
$C_{13}C_{15}C_{14}$	120.3		118.6	121.9
$C_{13}C_{15}X_{25}$	119.8		120.7	117.0
$C_{15}N_{25}H_{29}$	–		116.6	127
$C_3C_{11}H_{21}$	119.9		119.7	122
$C_{11}C_{13}H_{23}$	119.7		119.8	120
Dihedral angles (deg)				
$O_4S_1C_3C_{11}$	23.3	28.1	23.7	
$C_{13}C_{15}N_{25}H_{29}$	–		−22.1	
$C_{11}C_{13}C_{15}X_{25}$	−179.9		−177.3	
$C_3S_1C_2C_6$	90.4	86.6	90.2	
Rotational constants (GHz)				
A	0.9262		0.7233	
B	0.3810		0.2483	
C	0.3583		0.2228	
Dipole moments (D)				
μ	5.65		6.57	

Table 2. Calculated total energies E (in Hartrees) of possible structures together with energy differences ΔE (kcal mol^{-1}) to the corresponding lowest-energy structures of diphenylsulfone and Dapsone at DFT-B3LYP and MP2 (both using a 6-311G** basis set) levels of theory[a].

Structure	(φ_1, φ_2)[a]	E (H)	ΔE (kcal mol^{-1})
	Diphenylsulfone (DFT-B3LYP)		
perpendicular	(90°,–)	−1012.047919	0.00
co-planar	(0°,–)	−1012.009099	24.36
	Diphenylsulfone (MP2)		
perpendicular	(90°,–)	−1009.739657	0.00
co-planar	(0°,–)	−1009.694498	28.34
	Dapsone (DFT-B3LYP)		
perpendicular	(90°,21°)	−1122.799697	0.00
NH_2 inversion TS[a]	(90°,0°)	−1122.798046	1.04
co-planar (TS[a])	(0°,0°)	−1122.756879	26.87
	Dapsone (MP2)		
perpendicular	(90°,26°)	−1120.197216	0.00
NH_2 inversion TS[a]	(90°,0°)	−1120.191453	3.62
co-planar (TS[a])	(0°,0°)	−1120.144670	32.97

[a] φ_1 denotes the torsional angle CCSO and φ_2 the torsional angle HNCC; "perpendicular" denotes the conformer with $\varphi_1 = 90°$, "co-planar" that with $\phi_1 = 0°$; TS stands for the planar transition state of the NH_2 inversion.

Although only DFT structural parameters are listed in Table 1, in the absolute minimum structures of both molecules there is not much a difference between DFT and MP2 results. The OSC bond angle of about 107° is reasonably close to the expected tetrahedral angle at the sulfur atom. The absolute minimum is termed perpendicular, because the CSCC dihedral angle (being the angle between the C_3S_1 and the C_2C_6 bonds, projected onto a plane perpendicular to the S_1C_2 bond, or – both are equal – the angle between the C_2S_1 and the C_3C_{12} bonds, projected onto a plane perpendicular to the S_1C_3 bond) in both structures is almost 90°. Thus the planes of the phenyl rings in the minimum face each other in an almost C_{2v} symmetry. As explained in the Introduction, the situation at the -NH_2 groups in Dapsone is – as expected – very similar to the corresponding one in our previously published results on chlorine-substituted anilines [5], with a pyramidal -NH_2 group having both hydrogens on the same side of the corresponding phenyl ring.

Since the S(3d)O(2p) π bonds are in the same plane as the SO_2 group, the lone pairs on the oxygen atoms are perpendicular to the plane, and thus point into the space above a phenyl ring, but are situated quite far away from the ring plane. Thus, although one cannot exclude that some back-donation of electrons between lone pairs and the antibonding ring π^* orbitals might occur (negative hyperconjugation), we expect its effect on the structure of the system, if present at all, not to be too large.

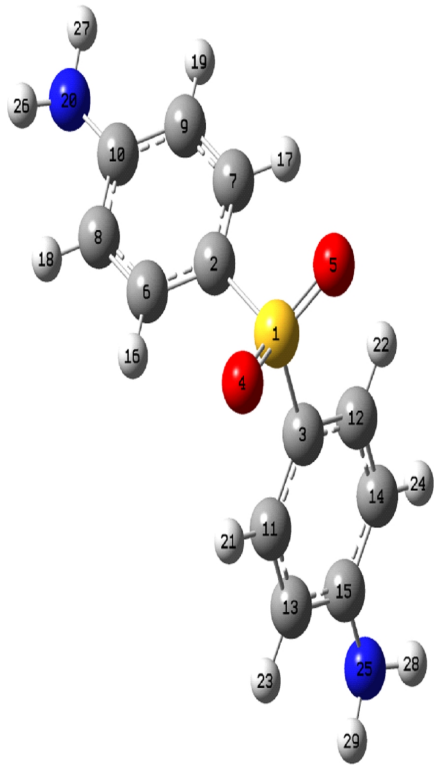

Fig. 1. Atom numbering and DFT-optimized structure for Dapsone (in case of diphenylsulfone $N_{20}H_{26}H_{27}$ are replaced by H_{20} and $N_{25}H_{28}H_{29}$ are replaced by H_{25}).

In Table 1 we include for comparison a few experimental data we found in the literature for diphenylsulfone, and it is obvious that these agree reasonably well with our calculated ones. The structural data given in the table were calculated using DFT with a B3LYP (Becke-3-Lee-Yang-Parr) potential and a valence triple zeta basis augmented by polarization functions (6-311G**). From the X-ray data for Dapsone in reference [8] there is fair agreement between our calculated and the experimental structural data. What regards the phenyl rings, in a previous paper we compared calculated structures (with a somewhat smaller valence double zeta basis set, 6-31G**) [9] with experimental data for biphenyl, again finding reasonable agreement. Thus one can conclude that our computational method should be well applicable to Dapsone and diphenylsulfone. Also the reasonable agreement between calculated and experimental wavenumbers (as detailed in Tables 3 and 4) for the two systems makes us confident that our data can be trusted.

Table 3. Calculated (dp denotes calculated depolarization ratio) and observed wavenumbers (Infrared and Raman spectra) [21, 22] together with the ratio of observed to calculated wavenumbers (always with the observed infrared wavenumbers if possible) and the assignment of the vibrations to atomic motions based on the program GAUSSVIEW for diphenylsulfone (C_{2v}: 20 A_1 + 15 A_2 + 20 B_1 + 14 B_2 = 69 modes) where def. stands for deformation, (+) or (−) indicates that the corresponding motions in one ring are added or subtracted from those in the other ring, s denotes symmetric, as antisymmetric.

		— Wavenumber (cm^{-1}) —		obs./calcd.	Assignment
Symm.	calcd. (dp)	Infrared[a]	Raman[a]		
B_2	117 (0.75)		111 (w)	0.95	SO_2 rock + ring def. (−)
A_2	199 (0.75)		185 (vw)	0.93	SO_2 scissor + ring def. (−)
A_1	241 (0.60)		249 (w)	1.03	CSC bend + ring def. (−)
B_2	296 (0.75)		302 (w)	1.02	CS as stretch
A_1	305 (0.11)		313 (w)	1.03	CS s stretch
A_2	324 (0.75)		334 (vw, shd)	1.03	SO_2 scissor − ring def. (+)
B_1	453 (0.75)		462 (vw)	1.02	S − ring in plane bend
A_1	558 (0.31)	559 (vs)	568 (vw)	1.00	SO_2 bend + ring def. (+)
B_2	594 (0.75)	585 (vs)		0.98	$\alpha CH_2 + \beta CH_2$ s wag (−)
A_2	628 (0.75)	601 (vw)	611 (vw)	0.96	in plane as ring def. (−)
B_2	700 (0.75)	681 (s)		0.97	$\alpha CH_2 + \gamma$CH s wag (−)
B_2	730 (0.75)	734 (vs)		1.01	in plane s ring def. (−)
B_2	764 (0.75)	766 (s)		1.00	CS as stretch
B_2	937 (0.75)	936 (vw)		1.00	$\alpha CH_2 - \beta CH_2 - \gamma$CH s wag (−)
A_1	1013 (0.01)	1000 (m)	994 (vs)	0.99	as in plane ring def. (−)
B_2	1015 (0.75)		1015 (w)	1.00	as in plane ring def. (−)
A_1	1039 (0.07)	1032 (vw)		0.99	ring breathing (+)
A_1	1064 (0.72)	1064 (w)	1068 (vw)	1.00	$\alpha CH_2 - \beta CH_2$ s in plane bend (+)
B_2	1098 (0.75)	1106 (s)		1.01	$\alpha CH_2 - \beta CH_2$ s in plane bend (−)
B_1	1101 (0.75)		1143 (m)	1.04	$\alpha CH_2 - \beta CH_2$ as + γCH in plane bend (+)
A_1	1126 (0.03)	1160 (vs)		1.03	SO s stretch
B_1	1185 (0.75)	1186 (w)	1185 (vw)	1.00	$\alpha CH_2 - \beta CH_2$ as – γCH in plane bend (+)
B_1	1288 (0.75)	1293 (s)	1291 (s)	1.00	SO as stretch
B_1	1332 (0.75)	1314 (vs)		0.99	ring in plane as def. (+)
B_1	1347 (0.75)	1324 (s)		0.98	ring in plane as def. (+)
B_1	1479 (0.75)	1447 (s)		0.98	ring in plane as def. (+)
B_2	1506 (0.75)	1479 (vw)		0.98	ring in plane as def. (−)
A_2	1625 (0.75)		1568 (m)	0.96	SC_2 scissor + ring def. (−)
A_1	1625 (0.49)	1585 (vw)		0.98	ring in plane s def. (+)
B_1	1630 (0.75)	1617 (vw)		0.99	ring in plane s def. (+)
B_2	3170 (0.75)	2979 (vw)	2983 (vw, shd)	0.94	$\alpha CH_2 - \beta CH_2$ s +γCH stretch (−)
A_1	3170 (0.71)	3000(vw)		0.95	$\alpha CH_2 - \beta CH_2$ s +γCH stretch (+)
A_2	3181 (0.75)		3047(s)	0.96	$\alpha CH_2 - \beta CH_2$ as stretch (−)
B_1	3181 (0.75)	3064(vw)	3057(w)	0.96	$\alpha CH_2 - \beta CH_2$ as stretch (+)
B_2	3191 (0.75)	3096(vw)		0.97	$\alpha CH_2 - \beta CH_2$ s −γCH stretch (−)

[a] Intensities: v = very, w = weak, m = medium, s = strong, shd = shoulder. From measured peak heights these are: $0 < vw < 20\,\%$, $20 < w < 40\,\%$, $40 < m < 60\,\%$, $60 < s < 80\,\%$, $80 < vs < 100\,\%$, percentage of peak height of the strongest line.

In our opinion the large energy differences between co-planar (phenyl planes parallel to the SO_2 plane) and perpendicular (phenyl planes perpendicular to the SO_2 plane) geometries should be mostly due to steric effects (see Table 2 for a definition of these geometries). Any rotation of a phenyl ring out of the perpendicular arrangement would lead to the hydrogens of the rotated ring pointing to the other ring plane with rather close distances. Thus even the rotation of only one ring out of the perpendicular arrangement should increase the energy of the structure. This effect becomes far more dramatic in the co-planar structure, where the hydrogens of the two rings are at close distance and thus in a highly repulsive geometry, indicated by the large energy differences between planar and perpendicular structures. The differences between DFT and MP2 relative energies have their reason in our case in the fact that we are dealing with non-bonding interactions, and it is well known that DFT is not too accurate in the calculation of energy differences due to such effects.

Vibrational Wavenumbers, Spectra and Assignments of Normal Modes

The optimized structural parameters of diphenylsulfone and 4,4′-sulfonyldianiline were used to calculate

Table 4. Calculated (dp denotes calculated depolarization ratio) and observed wavenumbers (Infrared and Raman spectra) [17] together with the ratio of observed to calculated wavenumbers (always with the observed infrared wavenumbers if possible) and the assignment of the vibrations to atomic motions based on the program GAUSSVIEW for 4,4′-sulfonyldianiline (Dapsone, C_{2v}: 23 A_1 + 18 A_2 + 20 B_1 + 20 B_2 = 81 modes) where def. stands for deformation, (+) or (−) indicates that the corresponding motions in one ring are added or subtracted from those in the other ring, s denotes symmetric, as antisymmetric.

		— Wavenumber (cm^{-1}) —		obs./calcd.	Assignment
Symm.	calcd. (dp)	Infrared[a]	Raman[a]		
A_1	32 (0.72)		32 (ms)	1.00	CSC bend
B_2	107 (0.75)		107 (m)	1.00	SO_2 rock + ring def. (−)
A_1	168 (0.39)	178 (ms)		1.06	CSC bend + ring def. (−)
A_2	179 (0.75)		184 (w)	1.03	SO_2 scissor + ring def. (−)
B_2	258 (0.75)		276 (w)	1.07	SO_2 rock + ring def. (+)
B_2	299 (0.75)		296 (m)	0.99	CC as stretch
B_1	335 (0.75)		335 (vw)	1.00	NH_2 torsion (+)
B_1	370 (0.75)	383 (w)	390 (vw)	1.05	NH_2 torsion + ring def. (+)
A_2	409 (0.75)	410		1.00	NH_2 − ring in plane bend (−)
A_2	417 (0.75)	420 (vw)		1.01	ring twisting (−)
B_1	420 (0.75)		424 (w)	1.01	ring twisting (+)
B_1	472 (0.75)		500 (w)	1.06	CSC rock + in plane ring def. (+)
A_1	491 (0.11)	510 (vw)	514 (w)	1.04	SO_2 bend + ring def. (+)
A_1	508 (0.69)	545 (vs)		1.07	CS wag + NH_2 wag (+)
B_2	521 (0.75)	555 (s, shd)		1.07	CS wag + NH_2 wag (−)
A_1	554 (0.34)		577 (w)	1.04	SO_2 bend − ring def. (+)
A_1	640 (0.55)	633 (w)	637 (ms)	0.99	CS s stretch
A_2	647 (0.75)	648 (w)	654 (w)	1.00	SC_2 scissor + in plane ring def. (−)
B_2	685 (0.75)	696 (vs)	701 (m)	1.02	CS as stretch + ring def. (−)
B_2	719 (0.75)	727 (vs)		1.01	CS wag − NH_2 wag (−)
A_1	829 (0.08)	825 (s)	819 (s, shd)	1.00	ring breathing (−)
A_1	843 (0.03)		839 (vs)	1.00	ring breathing (+)
B_2	949 (0.75)	950 (w)		1.00	$\alpha CH_2 - \beta CH_2$ s wag (−)
A_1	956 (0.43)	960 (w)		1.00	$\alpha CH_2 - \beta CH_2$ s wag (+)
B_1	970 (0.75)	969 (w)	970 (vw)	1.00	$\alpha CH_2 - \beta CH_2$ as wag (+)
A_1	1017 (0.43)	1009 (m)	1008 (w)	0.99	in plane ring def. (+)
A_1	1062 (0.47)	1071 (vs)	1073 (vs)	1.01	SO s stretch + ring breathing (+)
A_1	1124 (0.10)	1103 (vs)	1107 (vs)	0.98	SO s stretch − ring breathing (+)
B_1	1151 (0.75)	1146 (vs)	1141 (vvs)	0.99	ring def. (+)
B_1	1278 (0.75)	1278 (vs)	1282 (w)	1.00	SO as stretch
A_2	1322 (0.75)	1291 (m, shd)		0.98	$\alpha CH_2 - \beta CH_2$ as bend (−)
A_1	1323 (0.08)	1336 (w)		1.01	$\alpha CH_2 - \beta CH_2$ s bend (+)
B_1	1362 (0.75)	1430 (m)	1440 (vw)	1.05	in plane ring def. (+)
B_1	1465 (0.75)	1496 (m)	1500 (ms)	1.02	in plane as (C–C bonds in opposite edges of the ring stretch differently) ring def. (−)
B_2	1529 (0.75)	1585 (s)		1.04	in plane as ring def. (−)
A_1	1530 (0.51)		1598 (vvs)	1.04	in plane as ring def. (−)
B_2	1639 (0.75)	1626 (s)		0.99	in plane s (C–C bonds in opposite edges of the ring stretch in the same way) ring def.(−)
A_1	1640 (0.35)		1635 (m)	1.00	in plane s ring def. (+)
B_1	3162 (0.75)	3045 (w)	3044	0.96	βCH_2 as stretch (+)
B_2	3163 (0.75)	3050 (w)	3059	0.96	$\alpha CH_2 - \beta CH_2$ s stretch (−)
A_1	3163 (0.11)		3073 (m)	0.97	$\alpha CH_2 - \beta CH_2$ s stretch (+)
A_1	3577 (0.12)	3445 (m)		0.96	NH_2 s stretch (+)
A_2	3678 (0.75)		3464 (w)	0.94	NH_2 as stretch (−)

[a] Intensities: v: very, w: weak, m: medium, s: strong, ms: medium to strong, shd: shoulder.

the vibrational frequencies of the ground state structures at the DFT-B3LYP/6-311G** level of calculation, since it is well known that DFT yields wavenumbers in rather good agreement with experiment. Assignments of the normal modes were carried out using the program GAUSSVIEW 3.0 for the stable conformers of the molecules instead of normal mode calculations as described previously [10, 11, 23]. The reason for the use of GAUSSVIEW is the presence of some vibrations containing out-of-plane movements of the

phenyl rings which lead to the fact that our set of internal coordinates for phenyl groups is incomplete, lacking ring carbon wagging coordinates needed to describe out-of-plane motions of a phenyl ring.

Discussion

The interesting properties and medicinal importance of 4,4′-sulfonyldianiline (Dapsone) as a sulfa drug [12 – 17] have turned our interest to investigate its structural stability in the present study. We extended the work to diphenylsulfone [18, 19] as the main building unit of the sulfa drug to understand the nature of the forces that control the conformational stability of such an important system. In an early study the characteristic vibrational modes of the -NH_2 and SO_2 groups and the aromatic ring have been assigned from isotopic shifts and studies in different solvents [17]. The determination of the molecular structure of Dapsone has shown that in the solid state it has a structure that slightly deviates from C_{2v} symmetry, with the benzene rings almost parallel to each other and both nearly perpendicular to the OSO plane [8] (see Table 2 for a definition of these geometries).

The vibrational modes of Dapsone were correlated by assuming C_{2v} symmetry of the molecule. In the present study we attempted to provide a more comprehensive structural and vibrational study of Dapsone by combining both theoretical and experimental data.

Diphenylsulfone and 4,4′-sulfonyldianiline in their perpendicular structure have C_{2v} symmetry. The 69 vibrational modes of diphenylsulfone span the irreducible representations $20\,A_1 + 15\,A_2 + 20\,B_1 + 14\,B_2$ in C_{2v}, while for 4,4′-sulfonyldianiline the 81 vibrational modes span the irreducible representations $23\,A_1 + 18\,A_2 + 20\,B_1 + 20\,B_2$ in the same group. The following discussion is focused only on the assignments of the intense spectral lines that characterize both molecules (see Tables 3 and 4 for experimental Raman spectra in the solid state as provided by Sigma Aldrich). The IR band positions and Raman line wavenumbers for diphenylsulfone were measured out in the spectra from the links: http://www.aist.go.jp/RIODB/SDBS NO. 1420 for the Infrared spectrum [21] and from sigmaaldrich.com for the Raman spectrum (both in the solid state or solution) [22]. The experimental information in Table 4 for Dapsone was taken from ref. [17]. Note, that the agreement in measured and calculated wavenumbers cannot be too good, because the molecules in the calculations are in the gas phase, while the experimental spectra were recorded in condensed phase leading to intermolecular interactions not present in the calculated models.

There appears an A_1 mode around 560 cm^{-1} which is very strong in the Infrared but very weak in the Raman spectrum and can be assigned to SO_2 bend coupled with a ring deformation. The line (only in the Infrared spectrum) at about 590 cm^{-1} is again very strong and could be identified as the theoretical α-$CH_2 + \beta$-CH_2 symmetric wag. The next strong band in the infrared around 690 cm^{-1} is α-$CH_2 + \gamma$-CH_2 symmetric wag. At around 730 cm^{-1} there follows a band which is very strong in the infrared and corresponds to a symmetric in plane ring deformation. Also, as expected, the SC_2 antisymmetric stretch is strong in the infrared at around 765 cm^{-1}. CH in-plane bends are a strong feature again in the infrared around 1100 cm^{-1}, while at 1160 cm^{-1} a very strong band appears which is SO_2 symmetric stretch, while the antisymmetric one is strong both in the Infrared and the Raman spectra around 1192 cm^{-1}. Up to about 1500 cm^{-1} three strong to very strong features appear in the Infrared, but not in the Raman spectrum, which are all in plane antisymmetric ring deformations. The rest of the features in the spectra are all very weak to medium, while α-$CH_2 - \beta$-CH_2 antisymmetric stretch at 3047 cm^{-1} is strong in the Raman spectrum. All other lines are very weak. The obs./calc. ratios (when possible based on observed infrared bands) are between 0.93 and 1.04 as to be expected, besides the lowest wavenumber (experimental) line at 111 cm^{-1} with 0.76. However, such low wavenumber features are usually plagued by anharmonicities which are not corrected for in our calculations.

In the case of Dapsone there are many similar features, however, with contributions from the -NH_2 groups in *para* positions. The experimental line positions are taken from ref. [20]. However, the assignments there, based just on similarities with other molecules, seem to be questionable to us, especially the assignment of the 107 cm^{-1} line in the Raman spectrum as a lattice mode, when the sample is in Nujol, *i. e.* without any crystal lattice, while we assign it to SO_2 rock with ring deformation, just as the 111 cm^{-1} line in diphenylsulfone, which we trust more, especially as the SO_2 scissor with ring deformation appears at practically the same wavenumber (184 and 185 cm^{-1}) in both molecules – which

in [20] is assigned as torsional mode. The torsions are not observed because according to our calculations they appear at extremely low wavenumbers around 10 cm^{-1}.

The strong vibrations with major NH_2 contributions in Dapsone are NH_2 wagging modes together with SC_2 wagging, which are very strong infrared features at 545 and at 555 cm^{-1}, the latter one being a strong shoulder. Another very strong infrared band is also NH_2 wagging together with SC_2 wagging at 727 cm^{-1}. Finally, at 3445 cm^{-1} in the Infrared (medium intensity) and at 3464 cm^{-1} (weak intensity) in the Raman spectrum the NH_2 symmetric and antisymmetric stretches are observed. Regarding normal modes which do not include NH_2 contributions the Dapsone spectrum is rather similar to that of diphenylsulfone discussed earlier.

However, there is one remarkable difference between certain modes of the two molecules. These are normal modes in which the two phenyl rings behave as if they are the strings of two coupled pendula fixed at the sulfone group with a mass at their freely swinging ends, the *para* positions in the rings. The big difference here is that in case of the drug Dapsone the freely swinging mass (NH_2) is about 16 times heavier than the one in diphenylsulfone (H) which – to our knowledge – shows no to only negligible medical activity. These vibrations are low energy ones at 47, 147, and 241 cm^{-1} in diphenylsulfone, and at 32, 97, 158, and 365 cm^{-1} for Dapsone. The remarkable difference between the two molecules is that in these normal modes the heavier mass at the ends of the "pendula strings" enforces a much larger out of plane bending than the H atoms can in diphenylsulfone. Likewise, in Dapsone there are two out of plane ring twisting vibrations at 420 and 424 cm^{-1}, which do not occur in the parent diphenylsulfone. Besides the fact that due to the NH_2 groups the aromatic ring systems in Dapsone should be somewhat more rich in electrons than in the parent, this higher structural flexibility of the phenyl rings in the drug Dapsone than in the non-drug diphenylsulfone could be a hint that this higher flexibility might be a – probably minor (see below) – reason for the drug activity of Dapsone, in that a molecule with more structural flexibility might fit better into receptor sites in cell membranes. This is probably a minor effect for the drug efficiency of Dapsone, since hydrogen bonding should play a far bigger role, while the probably most important fact is the lipophilic nature of Dapsone in contrast to other similar molecules [24], because *Mycobacterium leprae* contains large amounts of unusual lipids in its cell wall, making it more permeable to Dapsone [24].

Conclusion

We have made a full assignment of the vibrational spectra of Dapsone and diphenylsulfone to the movements of atoms in the normal modes, using the program GAUSSVIEW. However, a setback of this method is that it does not provide numerical evidence for the assignment. On the other hand, a PED (Potential Energy Distribution) calculation could overestimate the relative importance of certain symmetry coordinates in a normal mode. This is due to the fact that a symmetry coordinate with a relatively large force constant could lead to large PED contributions already at small displacements. Thus we propose that in the future symmetry coordinate calculations should be performed to obtain numerical evidence for the assignment of normal modes to symmetry coordinates. However, this evidence should not be based on PED values but rather on the expansion coefficients of a normal mode in terms of symmetry coordinates, since trustworthy vibrational assignments are very important to identify occurring atomic motions on a quantitative basis on the one hand, and on the other hand to identify reaction mechanisms by carefully monitoring changes in vibrational spectra due to chemical reactions, knowing which atomic motions cause a given vibrational line. For our systems, we have found that the drug Dapsone has a larger structural flexibility in its phenyl rings than the parent compound. This leads to the speculation that this flexibility in the phenyl rings might allow the drug to fit better into receptor sites in cell membranes. However, as detailed above, we assume this structural flexibility to play at best a minor role in the drug activity of Dapsone, if at all. Currently we study a similar molecule as Dapsone, which has hydroxy groups instead of amino groups in the *para* positions of its phenyl rings. Since the mass of an OH group (17 amu) is not much larger than that of an NH_2 group (16 amu) this molecule should exhibit the same kind of structural flexibility as Dapsone if our speculation is right, because that molecule also shows medical activity. However, again as detailed above, structural flexibility probably plays only a minor role in the drug activity of Dapsone, the most important effects being the lipophilic nature of Dapsone [24] and its ability to form hydrogen bonds.

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